# MANIFEST PSYCHOPATHOLOGY AND URINE BIOCHEMICAL MEASURES (MULTIVARIATE ANALYSIS IN MANIC-DEPRESSIVE ILLNESS)

REPORT NUMBER: 68-32


NAVY MEDICAL
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WASHINGTON, D. C. 20390

*Reprinted from the Archives of General Psychiatry*
*January 1970, Volume 22*


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THE USE of psychiatric rating scales for quantifying symptoms and signs is a recent methodologic refinement in behavioral-biochemical correlative investigations of psychiatric patients. Small-sample longitudinal studies, wherein the patient acts as his own control, have shown a number of interesting psychochemical and psychoendocrine correlations that were not evident with earlier cross-sectional sampling techniques.[1-8] Also, multivariate analytic methods now permit both the recognition of intra-individual correlations and the generalization of these correlations into group patterns.[9] In this paper are presented the results of multivariate analyses of changes over time of manifest psychopathology, quantified by a psychiatric rating scale, and multiple urine biochemical measures in manic-depressive patients. This study attempts to exploit the power of multivariate analytic techniques to elucidate the role of biochemical factors in manic-depressive illness.

In earlier reports studies of several biochemical measures in manic-depressive illness were presented. Two rapidly cycling manic-depressive patients were studied in the hospital, untreated, through complete cycles by daily clinical assessment of cycle phase (manic, euthymic, or depressed) and by daily measurement of 24-hour urine volume, osmolality, creatinine, 17-hydroxycorticosteroids (17-OHCS), vanillylmandelic acid (VMA), kynurenine (KYN), and indoleacetic acid (IAA).[10,11] A third rapidly cycling patient was studied in the same manner, but 24-hour urine measures did not include KYN or IAA.[2] A summary of the previous findings on these patients is as follows:

Two of the three patients had decreased urine volume and creatinine excretion during depression. Changes in urine osmolality were variable. It appeared that the urine volume decreases were secondary to decreased fluid intake during depression and that the variable urine osmolalities were secondary to uncontrolled variations in sodium intake. In these two patients urine volume and creatinine correlated + 0.61 and + 0.88 over a 90-day period. Since the third patient had occasional incomplete urine collections, urine biochemical values for this patient were corrected to constant creatinine excretion.

In two patients 17-OHCS excretions decreased during the course of hospitalization. Mean 17-OHCS excretions during mania were significantly lower than during depression; this, however, occurred only during the latter one half of hospitalization. In the third patient there were no significant differences in 17-OHCS excretions between cycle phases. It was suggested that a heightened defensiveness during mania relative to depression influenced 17-OHCS excretions only after the patients had acclimated to the hospital, and that an interaction between intrapsychic ego defense strength and external milieu stresses was the determinant of adrenal-cortical activity during each cycle phase.

In all three patients, significant increases in mean VMA excretion occurred during mania compared to depression. There were also significant intra-individual differences between mean VMA excretions during different periods of mania in two patients, a higher excretion having occurred during pe-

Submitted for publication April 21, 1969.

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Opinions expressed are those of the authors and are not to be construed as necessarily reflecting the official view or endorsement of the Navy Department.

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riods of more intense physical activity. It appeared that amount and type of physical activity was the major factor related to the level of epinephrine and norepinephrine biosynthesis as reflected by VMA excretion.[13]

In the two patients in whom kynurenine (KYN) excretion was measured, mean values during depression were significantly lower than during mania. $^{14}$C-tryptophan infusions in these two patients during different phases of their cycles revealed increased radioactivity of urine KYN during the depressive phases. This finding suggested an increased metabolism of tryptophan via the KYN pathway during depression and supported the possibility of hydrocortisone induction of tryptophan pyrrolase, the rate-limiting enzyme in the metabolism of tryptophan to KYN, during depression.

Mean IAA excretion was increased in depression compared to mania in both patients in whom this metabolite was measured. An explanation postulated for this finding was the possibility of increased handling of tryptophan via the tryptophan transaminase pathway which, like the pyrrolase pathway, is inducible by hydrocortisone. There was, however, little supportive evidence for this explanation, which, therefore, remained speculative.

The changes in the multiple biochemical variables measured in these patients, when correlated with gross assessments of clinical state, highlighted the inherent intersubject and intrasubject differences in patterns of physiologic activity in manic-depressive illness. It was apparent from direct clinical experience with these patients that, although all three were diagnostically rapidly cycling manic-depressives, each had a unique clinical pattern associated with her illness. In anticipation of such differences, the clinical state of two of the three patients[10,11] was quantitated by use of a multidimensional psychiatric rating scale, so that multivariate analyses of the several components of behavior and the urine biochemical variables might be accomplished.

A brief clinical resume of each patient follows; longer resumes have been presented previously.[10] Both patients were in the hospital and were untreated for psychiatric illness during the study. Patient 1 was studied for 90 days and patient 2 for 65 days.

## Report of Cases

CASE 1.—A 62-year-old white woman had a 17-year history of cyclic mood changes with a 60-day periodicity. These began shortly after menopause. During the manic phases the patient was hyperactive around the clock. She talked forcefully and continuously about religion, attempted to organize church outings among the patients, and "pack-ratted" every movable object on the ward into her room. She ate fairly well, drank copious amounts of water, and slept about one hour per night.

During the depressive phases the patient stayed in bed around the clock, covered with blankets. She looked depressed and manifested extreme psychomotor retardation. Questions were answered, after considerable delay, with one or two words. She made no demands of patients or staff. She did not arise for meals, her fluid intake diminished considerably, and she slept 8 to 14 hours per night. Findings of her physical and laboratory examinations were entirely within normal limits.

CASE 2.—A 50-year-old white woman had a three-year history of cyclic mood changes with a periodicity of 6 to 12 weeks. During the manic phases she was verbose and expansive, her associations loosened, and she at times was combative without apparent provocation. She ate almost nothing and slept one or two hours per night. She had few of the asthma attacks present during previous admissions. She required one electroshock treatment on three separate occasions during manic phases to interrupt particularly destructive behavior. (The urine samples from these days were omitted.)

During the depressive phases she was almost mute. After considerable pause she gave one-syllable answers to questions. She incessantly paced back and forth in a small area, picked at her wrists, and smoked about 40 cigarettes per day. She would not eat unless fed, but slept four to eight hours per night. This patient evidenced clinically a considerably greater component of thought disorder than did patient 1.

## Method of Procedure

**Rating of Psychopathology.**—The Brief Psychiatric Rating Scale (BPRS)[14] was chosen to provide a daily quantitative record of clinical manifestations. It has been demonstrated to assess several relatively independent factors identified in depressive and schizophrenic illnesses,[15,16] thereby affording the possibility of measuring individual differences in both affect and thought-disorder components in manic-depressive illness. It has been shown to reflect changes in psychopathology over time.[16] Also,

it has been "computerized"[17] with programs for multivariate analyses already available. The BPRS was completed for each patient by two members of the nursing staff at the end of each eight-hour shift—8:00 AM, 4:00 PM, and midnight.

**Measurement of Biochemical Variables.**—Continuous 24-hour urine collections were made on each patient with 8:00 AM as the time of change. Each patient was asked to void at that time, and that specimen became the last of the previous day's collection. The urines were pooled in the refrigerator at 4 C on the collection day and were immediately frozen at −20 C after the specimen was complete. Analyses were performed within eight weeks after collection, a period sufficiently short to obviate decomposition of the metabolites measured. Urine osmolality was measured on a Fiske osmometer. Urine creatinine was determined by the standard method of Jaffe,[18] urine 17-OHCS by a modified method of Silber and Porter,[19] urine VMA by the method of Pisano et al,[20] urine KYN by the ion exchange method of Brown and Price,[10,21] and urine IAA by the chromatographic method of Armstrong et al,[22] followed by the colorimetric method of Fischl and Rabiah.[23]

The urine collections for the first patient were complete, since she was cooperative during all phases of her cycle; hence no correction factor for lost samples was applied to the values of the variables measured. The second patient, however, had a thought-disorder component sufficient to obviate complete cooperation, and occasional individual specimens were lost on some days. These losses were confirmed

**Table 1.—*Correlation Matrix of Interrater Reliabilities for the Sum of All 16 BPRS Items for Patient 1***

| Rater | | | | | |
|---|---|---|---|---|---|
| 2 | 3 | 4 | 5 | 6 | |
| +0.81 | +0.77 | +0.73 | +0.67 | +0.66 | 1 |
| | +0.79 | +0.77 | +0.65 | +0.63 | 2 |
| | | +0.73 | +0.75 | +.074 | 3 Rater |
| | | | +0.72 | +0.68 | 4 |
| | | | | +0.77 | 5 |

**Table 2.—*Composite Reliabilities for Individual BPRS Items, Total Score, and Major Symptom Factors for Patient 2***

| Item | Factor | Composite Reliability |
|---|---|---|
| 1 | Somatic concern | +0.78 |
| 2 | Anxiety | +0.90 |
| 3 | Emotional withdrawal | +0.95 |
| 4 | Conceptual disorganization | +0.97 |
| 5 | Guilt feelings | +0.90 |
| 6 | Tension | +0.96 |
| 7 | Mannerisms and posturing | +0.95 |
| 8 | Grandiosity | +0.75 |
| 9 | Depressive mood | +0.97 |
| 10 | Hostility | +0.90 |
| 11 | Suspiciousness | +0.74 |
| 12 | Hallucinatory behavior | +0.84 |
| 13 | Motor retardation | +0.85 |
| 14 | Uncooperativeness | +0.92 |
| 15 | Unusual thought content | +0.95 |
| 16 | Blunted affect | +0.94 |
| | Total score | +0.97 |
| 1 | Anxious-depression factor (Item 2, 5, 6, 9) | +0.97 |
| 2 | Hostile-suspiciousness factor (Items 6, 10, 11, 14) | +0.95 |
| 3 | Withdrawal-retardation factor (Items 3, 13, 16) | +0.96 |
| 4 | Thinking-disturbance factor (Items 4, 12, 15) | +0.96 |

**Table 3.—*Manic and Depressive BPRS Factors for Patients 1 and 2***

| | | Patient 1 | | Patient 2 | |
|---|---|---|---|---|---|
| Item | Factor | Mania | Depression | Mania | Depression |
| 1 | Somatic concern | +0.93 | +0.03 | +0.16 | +0.80 |
| 2 | Anxiety | +0.92 | +0.14 | +0.16 | +0.92 |
| 3 | Emotional withdrawal | +0.72 | +0.52 | −0.06 | +0.98 |
| 4 | Conceptual disorganization | +0.95 | −0.09 | 0.00 | +0.98 |
| 5 | Guilt feelings | +0.28 | +0.07 | −0.14 | +0.91 |
| 6 | Tension | +0.96 | −0.09 | +0.10 | +0.97 |
| 7 | Mannerisms and posturing | +0.95 | −0.01 | +0.02 | +0.97 |
| 8 | Grandiosity | +0.95 | −0.17 | +0.72 | +0.38 |
| 9 | Depressive mood | −0.16 | +0.81 | −0.13 | +0.97 |
| 10 | Hostility | +0.96 | −0.05 | +0.71 | +0.51 |
| 11 | Suspiciousness | +0.97 | +0.04 | +0.44 | +0.71 |
| 12 | Hallucinatory behavior | +0.40 | +0.35 | +0.05 | +0.36 |
| 13 | Motor retardation | −0.48 | +0.76 | −0.28 | +0.74 |
| 14 | Uncooperativeness | +0.97 | −0.01 | +0.18 | +0.87 |
| 15 | Unusual thought content | +0.94 | +0.10 | +0.03 | +0.98 |
| 16 | Blunted affect | +0.28 | +0.73 | −0.23 | +0.93 |

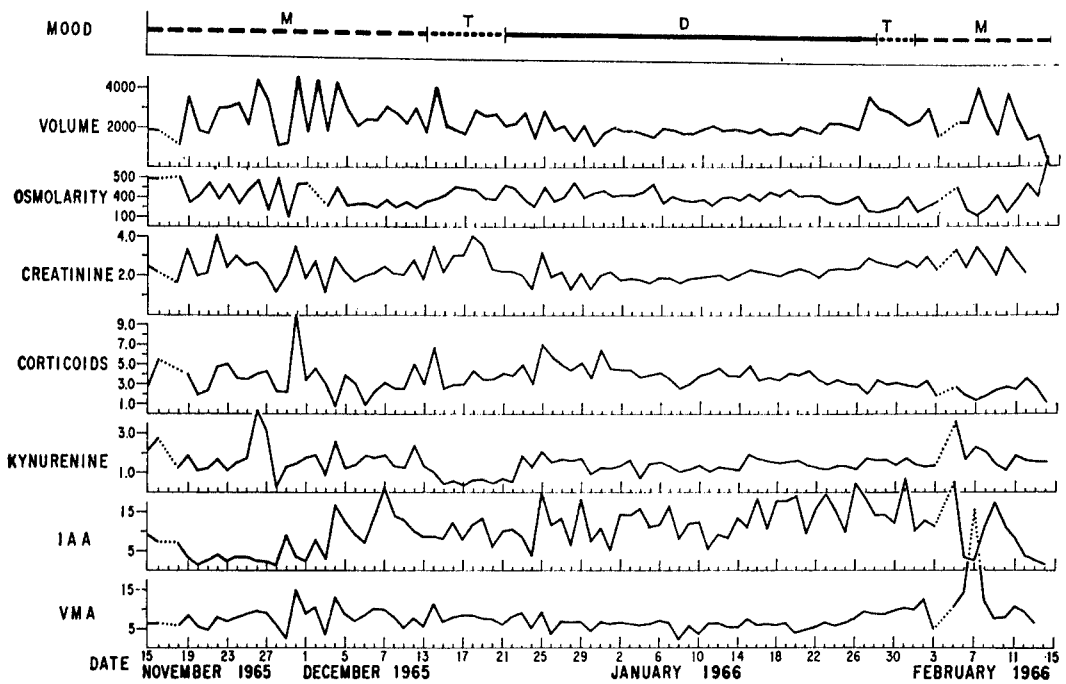



Fig 1.—Daily clinical ratings of mood and 24-hour urine biochemical variables for patient 1. **M** = mania; **T** = transition (euthymia); and **D** = depression.

by low urine volumes and creatinine values on these days without corresponding increases in osmolality. For patient 2, therefore, all values of the variables measured were corrected to 2.0 gm creatinine.

**Statistical Analyses.**—The question of what-changes-with-what over time was approached with multivariate correlational analysis techniques to attempt identification and descriptive summary of variables that appeared to change together within each patient. Factor analyses of correlations among BPRS symptom ratings over time served to identify clusters of symptoms that changed together. Multiple correlation and regression analyses were then done to evaluate the interdependence of the manic-depressive syndrome scores and the biochemical variables measured.

Statistical inferences from these analyses may be limited by uncertainty about degrees of freedom in the presence of possible serial dependencies of the individual measures.[24] The analyses were, however, undertaken in an attempt only to describe patterns of relationships over time within individual patients, so that problems of statistical inference can be considered not pertinent.

## Results

**Reliability of BPRS Ratings Made by Nurses.**—A preliminary analysis to evaluate the reliability of BPRS ratings made by the nursing staff was done by intercorrelating the independent ratings by the six nurses (two from each eight-hour shift) across days of observation for each patient separately. Table 1 is a correlation matrix of inter-rater reliabilities for the sum of all 16 BPRS items for patient 1. With the assumption that the reliable component of the ratings for each symptom was represented by a single principal factor, the reliability of a composite score obtained by averaging ratings made by the six nurses was estimated.[25] Table 2 lists estimated composite reliabilities for individual BPRS items, total score, and for major symptom factors for patient 2. Correlations among ratings by the nurses were so high that the 24-hour composite index of severity for each BPRS item was used in the subsequent analyses.

**BPRS Profiles.**—In an attempt to elucidate differences in BPRS profiles between the two patients, orthogonal powered vector factor analyses of correlations among BPRS symptom ratings over time were done. These analyses yielded the factor loadings shown in Table 3. The pattern of factor loadings for patient 1 indicated a manic factor with

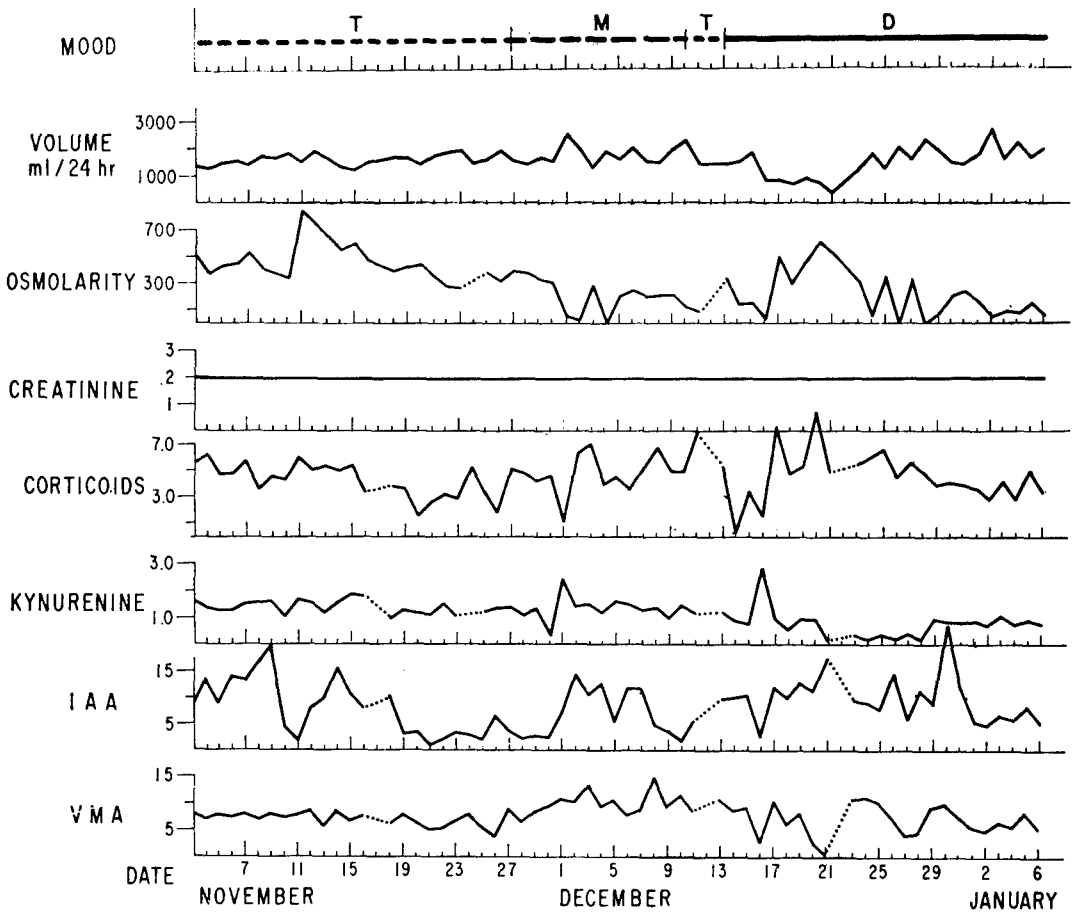



Fig 2.—Daily clinical ratings of mood and 24-hour urine biochemical variables for patient 2. **M** = mania; **T** = transition (euthymia); and **D** = depression.

high levels of disorganization, tension, motor manifestations, grandiosity, hostility, suspiciousness, uncooperativeness, and unusual thought content. For this patient the depressive factor was associated with heightened emotional withdrawal, motor retardation, and blunted affect.

The factor analysis of correlations among BPRS symptom ratings over time indicated quite a different picture for patient 2. The manic factor was associated with high levels of grandiosity, hostility, and suspiciousness. The depressive factor emphasized anxiety, emotional withdrawal, conceptual disorganization, guilt feelings, motor manifestations, and unusual thought content. In summary, the BPRS factor analyses revealed two distinctly different manic-depressive patterns. Patient 1 presented as a classic retarded depressive, whereas patient 2 appeared as an anxious, tense, disorganized depressive. The clinical impressions of the two patients are quite consistent with the empirically derived factor-analysis results, which provides support for the application of intra-individual factor analyses in this type of correlative research.

On the basis of these distinctly different factor results, two different "contrast functions" were defined to represent the major symptom shifts between manic and depressive phases for the two patients. In this context, a contrast function is a weighted combination of symptom variables measuring the relative prominence of the manic and depressive factors. For patient 1 the manic-depressive contrast function was defined as follows:

**Equation 1**

$$Y = X_{\text{Emot Withdr}} + X_{\text{Depr Mood}} + X_{\text{Motor Ret}} - X_{\text{Grandios}} - X_{\text{Host}} - X_{\text{Uncoop}}$$

For patient 2, the contrast function was defined as follows:

**Equation 2**

$$Y = X_{\text{Emot Withdr}} + X_{\text{Tens}} + X_{\text{Depr Mood}} - 1.5\,X_{\text{Grandios}} - 1.5\,X_{\text{HOSt}}$$

These contrast functions were used in the subsequent multiple correlation and regression analyses involving the biochemical measures.

**BPRS—Biochemical Interactions.**—Figures 1 and 2 show the clinical periods and daily values for all variables measured for patients 1 and 2 respectively. Correlations over time of the manic and depressive factors derived from the BPRS with the urine biochemical measures are shown for both patients in Table 4. For patient 1 the manic factor was associated with increases in VMA and KYN, and with decreases in 17-OHCS and IAA, while the depressive factor was associated with decreased osmolality. For patient 2 the manic factor was associated with increases in osmolality, VMA, and KYN. The depressive factor for this patient was associated with increased 17-OHCS, VMA, and IAA, and with decreased KYN. These correlations are similar to the previously reported comparisons between the mean values of these biochemical measures for each clinical phase of the patient's cycles.[10,11] These detailed findings are presented in order to evaluate better the results of the subsequent multivariate analyses.

A multiple-regression analysis was done for each patient in an attempt to ascertain what combination of biochemical measures correlated most highly over time with changes in the manic-depressive contrast function. Again, this method of analysis was applied solely for descriptive purposes. In both instances changes in the contrast function were found to be related to changes in the biochemical measures; the results were, however, different for the two patients who, as mentioned, also had quite different manic-depressive symptom configurations. For patient 1 (retarded depression), the standard regression equation defining that weighted combination of the five biochemical variables having the maximum correlation with the manic-depressive contrast function was as follows:

**Equation 3**

$$Y' = -0.05\,X_{\text{OSM}} + 0.51\,X_{\text{17-OHCS}} - 0.10\,X_{\text{VMA}} - 0.12\,X_{\text{KYN}} + 0.36\,X_{\text{IAA}}$$

For patient 1, 17-OHCS and IAA appeared most important in relation to changes in manic-depressive contrast, with KYN and VMA less influential. For patient 2 (agitated depression), the standard regression equation was as follows:

**Equation 4**

$$Y' = -0.37\,X_{\text{OSM}} + 0.15\,X_{\text{17-OHCS}} + 0.05\,X_{\text{VMA}} - 0.46\,X_{\text{KYN}} + 0.24\,X_{\text{IAA}}$$

For patient 2, osmolality, KYN, and IAA appeared most important with respect to changes in the level of manic-depressive contrast, with 17-OHCS less influential.

The pattern of weights assigned to the biochemical variables to achieve maximum correlation with the manic-depressive contrast function was different for the two patients. With the assumption of independence between successive days, conventional statistical tests would have revealed "significant" differences between the patterns of relationships. As mentioned earlier, however, we will not make this assumption but will only report descriptively that the observed BPRS-biochemical relationships for the two patients were substantially different. The similar pattern of signs, however, indicates that the same general direction of change occurred for both patients.

In order to examine the time sequence of the relationship between manic-depressive symptom changes and biochemical pattern changes, the manic-depressive contrast function scores for each patient (equations 1 and 2) were plotted over time along with the regression-derived composite of the biochemical variables (equations 3 and 4). Figure 3 shows the time-related changes in contrast function and composite biochemical measures for patient 1. With reference to the BPRS contrast function, there were consistently manic values in the first month of

**Table 4.—*Correlations of BPRS Manic and Depressive Factors With Urine Biochemical Variables for Patients 1 and 2***

| | Patient 1 | | Patient 2 | |
|---|---|---|---|---|
| Biochemical Variable | Mania | Depression | Mania | Depression |
| Osmolality | +0.13 | −0.31 | +0.27 | +0.14 |
| 17-OHCS | −0.39 | −0.02 | +0.11 | +0.19 |
| VMA | +0.42 | −0.02 | +0.61 | +0.26 |
| KYN | +0.24 | −0.10 | +0.65 | −0.50 |
| IAA | −0.33 | −0.06 | −0.03 | +0.24 |

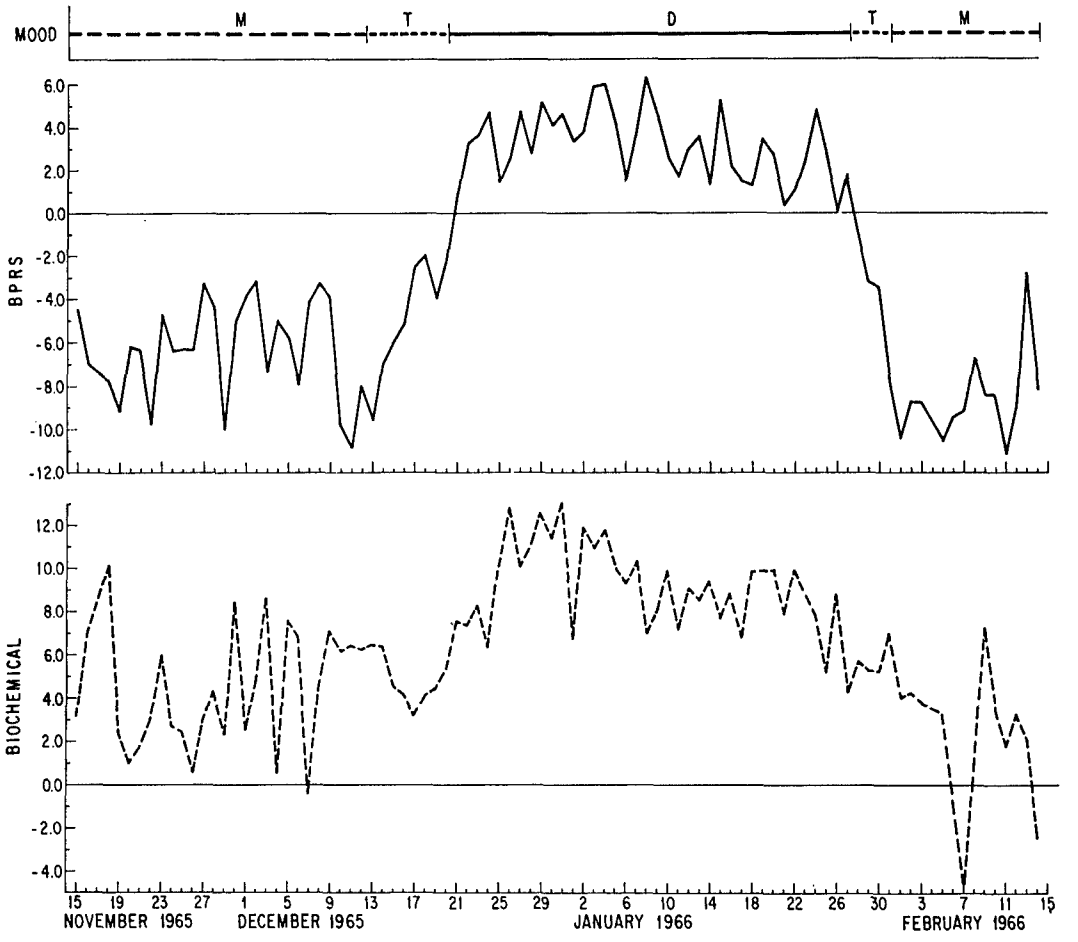



Fig 3.—Time-related changes in BPRS manic-depressive contrast function and regression-derived composite of biochemical variables for patient 1.

hospitalization and sharply shifting values from mania to depression from about Dec 11 to Dec 24. There was then a gradual decline in depressive values for about a month, a sharp decline in values from depression to mania from about Jan 27 to Feb 1, and manic values until the end of the study period. Although the shifts in BPRS contrast function values from mania to depression and later from depression to mania both occurred over periods of several days, there was a clinically recognized period of euthymia (eight days) only for the first BPRS shift.

With reference to the regression-derived function based on the biochemical variables for patient 1, the trends and shifts were similar to those of the BPRS contrast function; the dates of change were, however, several days later in each instance (Dec 11 vs 17, Dec 24 vs 26, Jan 27 vs 31, and Feb 1 vs 7).

Figure 4 shows the time-related changes in contrast function and composite biochemical measures for patient 2. With reference to the BPRS contrast function, there was a stable period in the first month of hospitalization wherein this patient was essentially symptom-free. (She had received a full course of electroconvulsive therapy [ECT] just prior to the study.) About Dec 28 a shift in contrast function values began, which coincided with a clinically recognized episode of mania. This trend continued in the same direction, however, when the patient changed clinically from mania to depression about Dec 10, increasing at a somewhat lesser rate during the depressive phase. Toward the end of this phase, about Dec 31, a gradual decline in BPRS values occurred.

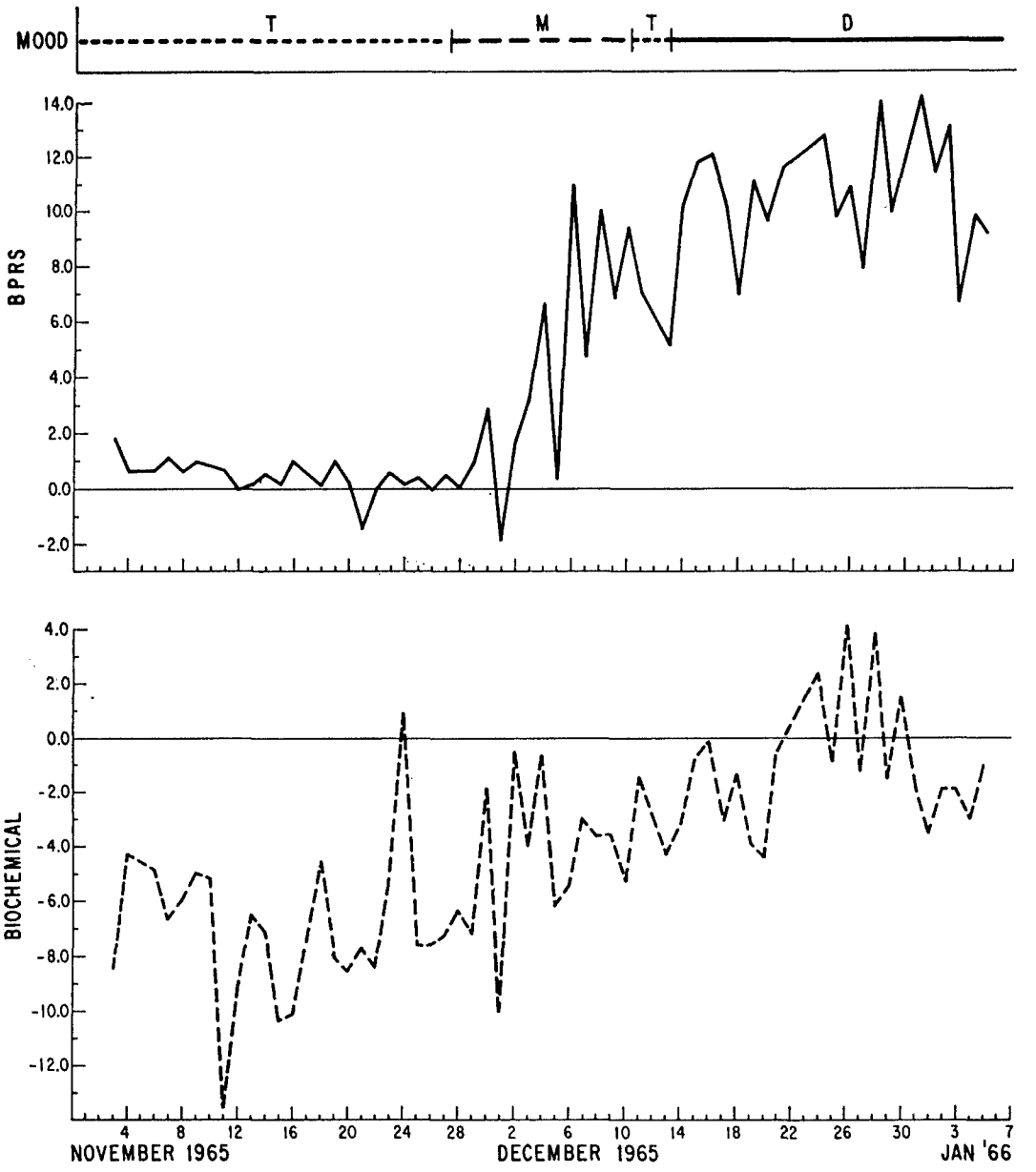



Fig 4.—Time-related changes in BPRS manic-depressive contrast function and regression-derived composite of biochemical variables for patient 2.

The regression-derived function based on the biochemical variables followed a pattern similar to the BPRS contrast function. Because the BPRS contrast function failed to distinguish clearly the clinical phases in this patient, no attempt will be made to compare the BPRS to the biochemical values. The discriminant analyses which follow, however, do permit this comparison.

In order to examine further the time sequence of relationships between manic-depressive symptom changes and biochemical pattern changes a different multivariate statistical model was employed. In the first set of analyses (Fig 3 and 4) the clinical assessment of the phase of the manic-depressive cycle was entirely disregarded. A multiple regression method was used to define the combination of biochemical measures that maximally correlated with changes in the

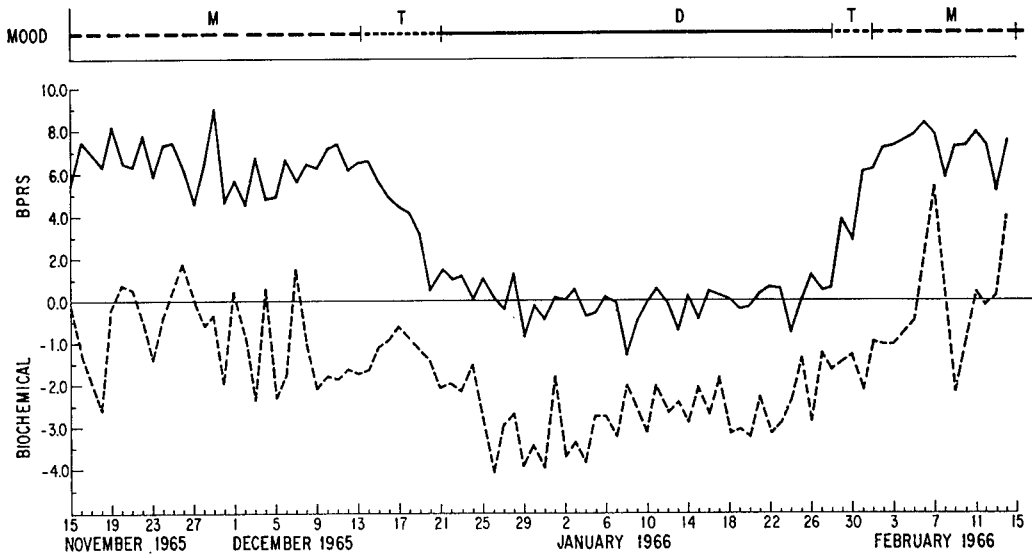
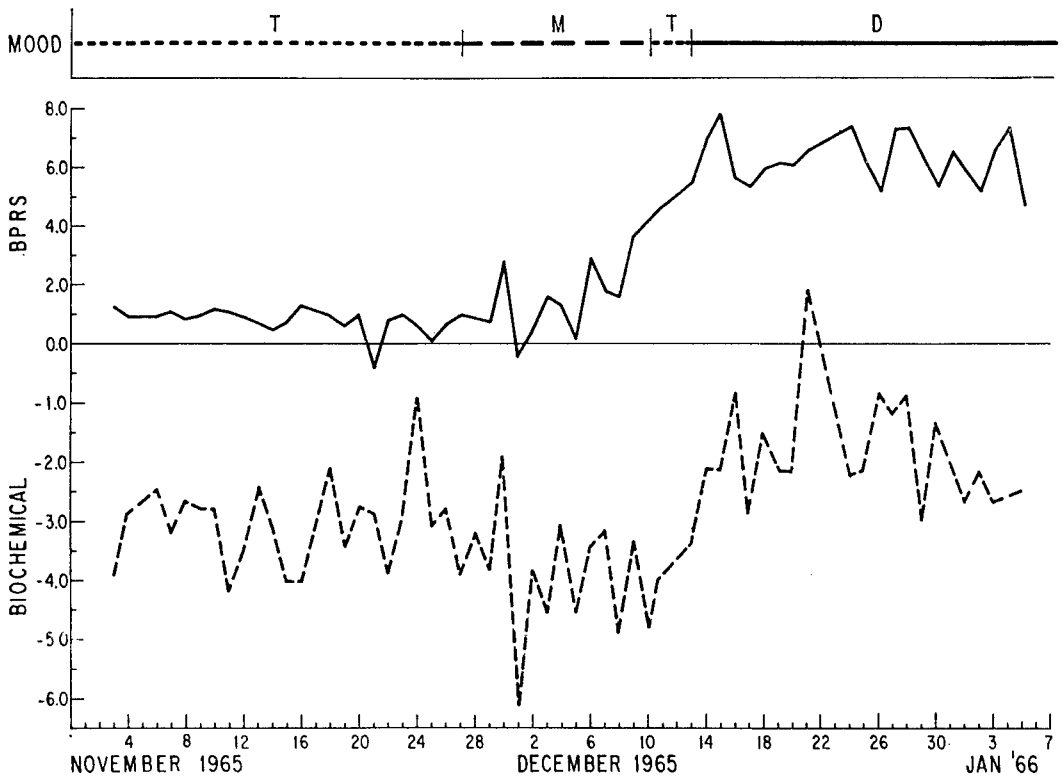



Fig 5.—Time-related changes in weighted combinations of BPRS items and of biochemical variables discriminating maximally between clinical mania and clinical depression for patient 1.

Fig 6.—Time-related changes in weighted combinations of BPRS items and of biochemical variables discriminating maximally between clinical mania and clinical depression for patient 2.



factor analysis-derived BPRS contrast function. In the second set of analyses, however, the clinical assessment of cycle phase was used as the criterion. Combinations of BPRS symptom ratings, on the one hand, and biochemical measures, on the other hand, were sought which would maximally discriminate between manic and depressive clinical phases.

The statistical method of discriminant analysis was used for deriving, independently from each other, the composite BPRS and composite biochemical functions.[26] Serial dependencies were disregarded, since the purpose was not to establish statistical significance, but to define weighted combinations of variables that maximally distinguished between the clinical phases. The determination of the biochemical discriminant function was independent from the determination of the BPRS discriminant function, permitting a different view of time-series relationships. For patient 1, the equations for BPRS and biochemical measures respectively were as follows.

**Equation 5**

$$Z = -0.30\,X_1 + 0.25\,X_2 - 0.47\,X_3 + 1.05\,X_4 - 0.44\,X_5 + 0.15\,X_6 - 0.78\,X_7 + 1.36\,X_8 - 0.37\,X_9 + 1.27\,X_{10} - 0.58\,X_{11} + 0.48\,X_{12} - 0.56\,X_{13} - 0.55\,X_{14} - 0.20\,X_{15} + 0.61\,X_{16}$$

($X_{1\text{-}16}$ = scores for BPRS items 1-16)

**Equation 6**

$$Z' = 0.00\,X_{OSM} + 0.70\,X_{17\text{-}OHCS} - 0.11\,X_{VMA} - 0.64\,X_{KYN} + 0.16X_{IAA}$$

For patient 2, these equations were as follows:

**Equation 7**

$$Z = 0.14\,X_1 - .85\,X_2 - 1.36\,X_3 + 1.03\,X_4 + 0.41\,X_5 + 1.15\,X_6 - 0.40\,X_7 - 1.27\,X_8 + 0.41\,X_9 - 0.71\,X_{10} + 1.26\,X_{11} + 0.29\,X_{12} + 0.52\,X_{13} - 0.52\,X_{14} - 0.01\,X_{15} + 0.70\,X_{16}$$

($X_{1\text{-}16}$ = scores for BPRS Items 1-16)

**Equation 8**

$$Z' = 0.00\,X_{OSM} + 0.12\,X_{17\text{-}OHCS} + 0.10\,X_{VMA} + 2.24\,X_{KYN} - 0.09\,X_{IAA}$$

As with equations 1 to 4, the patterns of weights assigned to the BPRS and biochemical variables in equations 5 to 8 were different for the two patients. Again, we will not assume independence between successive days in an attempt to establish statistically significant differences, but will only report descriptively that the BPRS-biochemical relationships for the two patients based on the discriminant analyses also were qualitatively substantially different.

Figure 5 shows the time-related changes in BPRS and biochemical values for patient 1. The same general trends as in Fig 3 are apparent, with the dates of trend change for the BPRS values again several days earlier than those for the biochemical values (Dec 14 vs 17, Dec 20 vs 26, Jan 24 vs 26, Feb 6 vs 7).

Figure 6 shows the time-related changes in BPRS and biochemical values for patient 2. Once again, the trend shifts in the BPRS values appear to have occurred several days prior to those for the biochemical values (Dec 5 vs 10, Dec 15 vs 21). Minimum BPRS values occurred in the period from Nov 20 to Dec 5, whereas minimum biochemical values occurred between Dec 1 and 11.

## Comment

The development of small-sample longitudinal research designs[27] necessitates the corresponding development of behavioral rating scales that retain their intrasubject reliability over time. Bunney and Hamburg[28] devised a 24-item rating scale permitting continuous 24-hour quantification of behavior in psychiatric patients, utilizing the nursing research team. Inter-rater reliabilities were quite high. Hargreaves and Blacker[29] factor analyzed the Bunney-Hamburg scale, identifying unique dimensions of change for each patient and suggesting their use in time-series analysis. Hargreaves[30,31] also modified the Bunney-Hamburg scale into a Nursing Rating Scale for more general patient use and devised an automatic keyboard for rating scales which feeds into a card punch, simplifying nurses' rating tasks and reducing clerical errors.

The BPRS data in the present study suggest that the BPRS also is a useful instrument for continuous 24-hour assessment of intra-individual symptom change over time and that it can be used effectively by nursing personnel. The high inter-rater correlations (Tables 1 and 2) indicate the substantial reliability of the nurses' ratings. Prepa-

ration of the raters consisted of showing the scale to the group of nurses, answering questions about the items before the study began, and requesting independent scoring by each nurse throughout the study. Overall et al[32] showed that factor analyses of nurses' and psychiatrists' BPRS ratings yielded very comparable factor structures, suggesting that nurses' ratings are accurate and useable in time-series analyses. Because the BPRS contains only 16 items, with a seven-point scale for each, it would be as easily set up on an automatic keyboard as the Bunney-Hamburg or Hargreaves scales.

The factor-analysis results for our patients show that the BPRS is a precise and sensitive indicator of both inter-individual differences in symptom constellations and intra-individual shifts in psychopathology in manic-depressive illness. The patterns of factor loadings for mania and depression permitted an objective and quantitative description of the differences in these cycle phases for the two patients, providing a considerable methodologic refinement over global clinical assessments of mania, euthymia, and depression. Distinguishable differences in BPRS profiles occurred between the clinical phases of each patient's cycle, so that manic-depressive contrast functions could be defined for use in time-series analyses.

The measurement of several biochemical parameters allowed biochemical factor-loadings for mania and depression to be similarly computed. The patterns of the biochemical factor-loadings, as did the BPRS patterns, permitted differentiation of the cycle phases for each patient. Persky et al[33] recently applied multivariate analyses to endocrine and affect measures in a sample of normal and emotionally disturbed men and defined an anxiety-depression (dysphoria) factor which correlated highly with a group of five measures of adrenocortical response. Our results indicate that multivariate biochemical reflections of psychopathology, intra-individually over time, can also be discerned. Bridges et al,[34] in a multivariate physiological and biochemical study of anxiety, noted individual differences in the relative responsiveness of the variables measured, suggesting that the stress levels of any single variable do not depend solely on the intensity of the evoking psychological state. The measurement of biochemical variables related to different metabolic systems, eg, adrenal-cortical hormones, catecholamines, and indole metabolites as in the present study, would appear to offer the best possibility of elucidating any individual differences in relative responsiveness of these variables.

The temporal relationship of changes in BPRS profiles to changes in biochemical variables was investigated by means of two different types of time-series plots. In the first, a manic-depressive contrast function was defined from the BPRS factor-analysis results to represent the major symptom shifts between mania and depression. This BPRS contrast function was plotted over time along with the regression-derived composite of biochemical measures correlating most highly with the BPRS contrast function. In the second, discriminant analyses were used to obtain a weighted combination of BPRS variables and a weighted combination of biochemical measures having maximally different values between the clinically defined manic and depressive phases, and these two combinations were plotted together over time.

For patient 1, both time-series plots (Fig 3 and 5) showed clear shifts in the BPRS function with cycle phases, which occurred several days earlier than the corresponding shifts in the biochemical function. This patient was different from patient 2 in several respects. First, she entered the hospital during a manic phase and had been untreated prior to the study, whereas patient 2 was initially in a temporary euthymic phase following a full course of ECT. Second, patient 1 demonstrated a rather classical clinical picture, being extremely hyperactive during mania, evidencing considerable psychomotor retardation during depression, and having a minimal thought-disorder component. Patient 2, on the other hand, was agitated and hyperactive during both mania and depression and had a considerable thought-disorder component to her illness. Third, complete urine collections with patient 1 permitted assay of true 24-hour levels of the biochemical variables, whereas occasional lost urine specimens from patient 2 necessitated introducing the error inherent in correcting

all her 24-hour biochemical values to 2.0 gm creatinine. The time-series plots for patient 1, therefore, differentiate clearly between mania and depression and are not subject to the special problems of patient 2. It appears from the data from patient 1 that biochemical shifts, as reflected in the excretion of urinary metabolites, were secondary phenomena with respect to shifts in manifest psychopathology between cycle phases. If changes in central nervous system biochemistry preceded shifts in psychopathology, they were not reflected in the urinary metabolites measured in this patient.

Neither time-series plot for patient 2 (Fig 4 and 6) showed the clear shifts in BPRS and biochemical functions between cycle phases that were evident for patient 1. As mentioned, patient 2 had several similar clinical features during both mania and depression, such that the BPRS contrast function distinguished between this patient's cycle phases primarily by changes in rate of trend rather than by changes in direction of trend. The discriminant analysis time-series plot for patient 2 (Fig 6), on the other hand, did reflect differences between the clinical phases and was similar in its temporal BPRS-biochemical relationship to the time-series plots for patient 1.

The most reasonable interpretation of the time-series data on our two patients would appear to be that the urine biochemical variables were peripheral reflections of alterations in metabolic pathways that were secondary to changes in specific central nervous system influences, such as ACTH release, and nonspecific changes, such as level of motor activity, occurring with shifts between mania and depression. It is quite possible that the cycling in manic-depressive illness results from biochemical changes in certain areas of the brain antecedent to the shifts in manifest psychopathology, but it is apparent that any such antecedent central nervous system (CNS) biochemical changes were not reflected in the urinary metabolites measured in this study. In future studies of manic-depressive illness measurement of biochemical variables that more clearly discriminate CNS metabolism from that of the rest of the body may yield time-series plots in which shifts in the biochemical domain precede shifts in manifest psychopathology.

**Summary**

The purpose of this study was to assess changes in manifest psychopathology in manic-depressive illness, as quantitated by a psychiatric rating scale, and concomitant changes in the levels of several urine biochemical variables. Two hospitalized rapidly cycling manic-depressive patients underwent daily ratings by a nursing staff using the Overall-Gorham Brief Psychiatric Rating Scale (BPRS) and daily 24-hour urine collections for assay of volume, osmolality, 17-hydroxycorticosteroids, vanillylmandelic acid, kynurenine, and indoleacetic acid. Multivariate analyses of the BPRS and biochemical data yielded the following results:

The BPRS was shown to be a useful instrument with which nursing staff can quantitate day-to-day changes in psychopathology in manic-depressive patients. Inter-rater reliabilities among nurses were quite high.

Factor analyses of the BPRS variables yielded specific manic and depressive symptom clusters for each patient. The first patient appeared as a retarded depressive, whereas the second patient appeared as an anxious, tense depressive. The clinical impressions of the patients were consistent with the factor analyses, providing support for the use of intra-individual factor analyses in longitudinal research designs.

A manic-depressive contrast function based on the factor-analysis data was defined for each patient. This was plotted over time together with a regression-derived composite of the five biochemical variables that correlated most highly with the BPRS contrast function. Also, for each patient discriminant analyses were used to define, independent of each other, weighted combinations of BPRS variables and of biochemical variables that maximally discriminated between the clinically defined periods of mania and depression for each patient. These BPRS and biochemical discriminant functions were also plotted together over time.

The time-series plots of the manic-depressive contrast function along with the correlated biochemical composite and the BPRS discriminant function along with the biochemical discriminant function revealed that for both patients shifts in the biochemical

variables generally lagged several days behind shifts in manifest psychopathology as measured by the BPRS.

It appears that the urine biochemical variables measured in this study were peripheral reflections of alterations in metabolic pathways secondary to specific CNS influences, such as ACTH release, and nonspecific changes, such as level of motor activity, occurring with shifts between mania and depression. It does not appear that the urine variables measured reflected any biochemical CNS changes antecedent to shifts in manifest psychopathology during the manic-depressive cycle.

This study was supported in part by California DMH grant No. 66-2-40.4 and by NIMH grant No. DHEW 1 RO MH 14675 (01). This is report No. 68-32, supported by the Bureau of Medicine and Surgery, Department of the Navy, under Research Work Unit MR011.01-6001.

Brian R. Clark, AB, Sudhir N, Dalal, MA, Joan Linger, RN, and the Neuropsychiatric Institute's 3-West Staff provided valuable technical assistance.

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*Printed and Published in the United States of America*

UNCLASSIFIED

Security Classification

## DOCUMENT CONTROL DATA - R & D

*(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)*

| 1. ORIGINATING ACTIVITY (Corporate author) | 2a. REPORT SECURITY CLASSIFICATION |
|---|---|
| Navy Medical Neuropsychiatric Research Unit<br>San Diego, California 92152 | Unclassified |
| | 2b. GROUP |

3. REPORT TITLE

Manifest psychopathology and urine biochemical measures (Multivariate analysis in manic-depressive illness.)

4. DESCRIPTIVE NOTES *(Type of report and inclusive dates)*

5. AUTHOR(S) *(First name, middle initial, last name)*

Robert T. RUBIN and John E. OVERALL

| 6. REPORT DATE | 7a. TOTAL NO. OF PAGES | 7b. NO. OF REFS |
|---|---|---|
| 1968 | 13 | 34 |

| 8a. CONTRACT OR GRANT NO. | 9a. ORIGINATOR'S REPORT NUMBER(S) |
|---|---|
| b. PROJECT NO. MR011.01-6001 | 68-32 |
| c. | 9b. OTHER REPORT NO(S) *(Any other numbers that may be assigned this report)* |
| d. | |

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This document has been approved for public release and sale; its distribution is unlimited.

| 11. SUPPLEMENTARY NOTES | 12. SPONSORING MILITARY ACTIVITY |
|---|---|
| | Bureau of Medicine and Surgery<br>Department of the Navy<br>Washington, D. C. 20390 |

13. ABSTRACT

Two hospitalized rapidly cycling manic-depressive patients underwent daily ratings by nursing staff using the Overall-Gorham Brief Psychiatric Rating Scale and daily 24-hour urine collections for assay of volume, osmolality, 17-hydroxycorticosteroids, vanillylmandelic acid, kynurenine, and indoleacetic acid.

Multivariate analyses of the BPRS and biochemical data. The BPRS yields useful day-to-day measures of changes in psychopathology in manic-depressive illness and delineates specific manic and depressive symptom clusters for each patient. Regression equations for the biochemical measures were constructed to yield a "predicted" contrast function correlating best with BPRS contrast function for each patient. Time-series plots were made with BPRS contrast function and biochemical "predicted" contrast function together, and with BPRS and biochemical discriminant combinations together. These time-series plots generally revealed that shifts in the biochemical domain lagged several days behind shifts in the BPRS domain. It appears that the urine biochemical variables were peripheral reflections of alterations in total body metabolic pathways secondary to both specific central nervous system influences, such as ACTH release, and non-specific changes, such as level of motor activity, occurring with shifts between mania and depression. It does not appear that the urine variables measured in this study reflected any biochemical CNS changes antecedent to shifts in manifest psychopathology during the manic-depressive cycle.

| 14. KEY WORDS | LINK A | | LINK B | | LINK C | |
|---|---|---|---|---|---|---|
| | ROLE | WT | ROLE | WT | ROLE | WT |
| Psychosis | | | | | | |
| Depression | | | | | | |
| Psychiatry | | | | | | |
| Therapy | | | | | | |
| Rating Scales | | | | | | |
| 17-Hydroxycorticosteroids | | | | | | |
| Psychopathology | | | | | | |
| Biochemistry | | | | | | |